REMARKS

1. Status

Claims 1, 13, 36, 41 as amended and claims 2-4, 6-7, 14-16, 18-19, 25-26, 28-31, 33-35, 37-40 and 42-45 are currently pending. Claims 8-12 and 20-24 have been withdrawn. Claims 5, 17, 27, and 32 have been canceled. The rejections set forth in the Office Action are traversed by amendment or by argument below. Support for the claim amendments can be found in the claims as originally filed and do not constitute new matter.

2. Rejections under 35 U.S.C. § 103 (a)

As an initial matter, and as previously noted in the response filed February 4, 2008, the Patent Office appears to have rejected the claims in part, in two separate rejections, rather than as a whole. The Patent Office has provided no clarification in the Advisory Action mailed March 19, 2008. As clearly stated in the M.P.E.P. 706.02 (j)

> *To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.* ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.*** *The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).* [emphasis added]

Thus, it is impermissible to make separate rejections based upon only part of the claims as the references when combined must teach all of the claim limitations. In this case, however, the Office has issued a first rejection of all of the claims based upon Bankneider in view of York and DiPiro in relation to claim limitations regarding topical administration of aldose reductase inhibitor to the dermis and epidermis. The Office has then issued a second, separate rejection of all of the claims over York, in view of Guideline No. 38, Chen and DiPiro in relation to the claim limitations regarding comparing efficacy of compositions against other useful agents.

If the combination of Bankneider, York and DiPiro is used to argue obviousness with regards to the claim limitations reciting topical administration of aldose reductase inhibitor to the dermis and epidermis, and the combination of York, Guideline No. 38, Chen, and DiPiro is used to argue obviousness with regards the claim limitations reciting comparing wound healing in the presence of the compounds, then in order to properly assert a *prima facie* obviousness determination against each of the claims taken as a whole requires the combination of all the asserted references (Bankneider, York, DiPiro, Guideline No. 38, and Chen). Despite the clear instructions set forth in the MPEP, the Office has not asserted this rejection, and has not considered each claim as a whole. Furthermore, the Patent Office did not respond to this issue or provide any clarification in the Advisory Action mailed March 19, 2008.

Thus, in the absence of any clarification from the Patent Office, and in an effort to expedite prosecution of these claims to allowance Applicants have amended the independent claims and will demonstrate in this response that even the combination of all five of these references still does not teach, suggest or make obvious **ALL** of the claim limitations of the amended independent claims. As a consequence, Applicants respectfully contend that the Office has not established a *prima facie* case of obviousness of pending independent claims 1, 13, 36, and 41 based on the cited references.

A. Claims 1-4, 6-7, 13-16, 18-19, 25-26, 28-31, 33-35 and 36-46 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Bankneider et al in view of York and DiPiro et al. The Applicants respectfully traverse the rejection.

According to M.P.E.P. 706.02 (j)

> *To establish a prima facie case of obviousness,* ***three basic criteria must be met****. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.* ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.*** *The teaching or suggestion to make the claimed combination and* ***the reasonable expectation of success must both be found in the prior***

***art and not based on applicant's disclosure**. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).* [emphasis added]

The Patent Office had previously asserted in the Action mailed November 2, 2007 that "the claims are directed to methods of identifying a compound for treatment of wounds to dermis or epidermis of external body surface in a diabetic animal, which also includes ophthalmic wounds." As Applicants have previously argued, this interpretation is incorrect as a matter of fact. First, the plain meaning of the claim language sets the metes and bounds of the claims as dermis or epidermis. There is no basis for including in this plain meaning wounds to the eye. This is evidenced by definitions and related diagrams of these terms from the "Medline Plus, Merriam Webster medical dictionary" and "Anatomy of the Eye": the skilled worker in the art would recognize that the eye is a specialized organ unique from the skin. The dictionary definition of the dermis is "the sensitive vascular inner mesodermic layer of the skin." The dictionary definition of "epidermis" is "the outer epithelial layer of the external integument of the animal body . . . that overlies the dermis." The dictionary definition of the eye is "an organ of sight, especially a nearly spherical hollow organ that is lined with a sensitive retina . . .." Applicant respectfully contends that there is no reference known to them that equates the eye with the skin, or teaches or suggests that the two organs are equivalent. None of the cited references make this claim

Applicants had previously, in the response filed February 4, 2008, requested, pursuant to 37 C.F.R. 1.104(d)(2), any reference within the knowledge of the Examiner or any other Patent Office employee that would support the asserted equivalence of skin and the eye. The Patent Office did not provide any such reference in the Advisory Action mailed March 19, 2008, nor did the Patent Office respond to Applicants' request.

Moreover, the Patent Office itself distinguishes between preparations for use on the skin (Subclass 78.06) and ophthalmic preparations (Subclass 78.04).

Furthermore, as noted in the M.P.E.P. 2173.01:

> *A fundamental principle contained in 35 U.S.C. 112, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as **>any special meaning assigned to a term is clearly set forth in the specification. See MPEP § 2111.01.< Applicant may use functional language, alternative expressions, **negative limitations**, or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought. As noted by the court in In re Swinehart, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of*

language used to define the subject matter for which patent protection is sought.

Thus, so long as the use of a term is not contrary to the understanding of the worker skilled in the art (and for the reasons set forth above Applicants respectfully contend it does not) an Applicant is permitted to delimit the use of a term such as dermis and epidermis as used in their claims. Applicants have clearly indicated in the application (Fig. 3 and Example 2), the previous response filed February 4, 2008, in this current response, and consistently in previous responses that they do not consider wounds to the dermis/epidermis to include ophthalmic wounds and have limited the definition of dermal/epidermal to the skin. Applicants thus respectfully contend that when their claims state dermis and epidermis, that is precisely what they mean.

In the Advisory Action mailed March 19, 2008, the Patent Office does not address this issue and does not reiterate their previous assertion (that the wounds to the dermis and epidermis encompass ophthalmic wounds). Thus, Applicant can only assume that, based upon Applicants' extensive arguments, the Patent Office no longer holds this interpretation. Thus, it appears that the Applicant and the Patent Office agree that the wounds recited in the claims are limited to "wound in the dermis or epidermis of a diabetic animal" and do not include opthalmic wounds and furthermore, that wounds to the dermis and epidermis are not the same as, and do not encompass opthalmic wounds.

With respect to the references cited with particularity by the Patent Office, Applicants note the following:

Independent claims 1, 13, 36, and 41 all recite the following claim limitations:

a) *producing* ***a wound in the dermis or epidermis*** *of a diabetic animal;*

b) *exposing the wound to an aldose reductase inhibitor compound by topical application of the compound to the wound,* ***wherein the topical application is to dermis or epidermis****;…* [emphasis added]

None of the references cited by the Patent Office teach, suggest, or make obvious the noted claim limitations of independent claims 1, 13, 36, and 41.

The Patent Office cites Bankneider et al., which teaches improved wound healing by oral or parenteral administration of an effective amount of tolrestat, an

aldose reductase inhibitor (abstract and column 1, line 61). Thus, as noted by the Patent Office, Bankneider "fails to administer his aldose reductase inhibitor topically [to] the epidermis or dermis wound." However, the Patent Office then asserts later in the instant Action that

> *the wounds created by Bankneider is on the skin and thus on the dermis or epidermis of the subjects. Accordingly, the limitation of treating wounds to the dermis/epidermis is met by the prior art reference*.

However, Bankneider administers the tolrestat systemically and the Patent Office admits that Bankneider "fails to administer his aldose reductase inhibitor topically [to] the epidermis or dermis wound." Thus, the Patent Office admits that Bankneider does **not** teach all of the claim limitations, namely, the topical administration of the aldose reductase inhibitor to the dermis or epidermis wound. It is well known to one of ordinary skill in the art that systemic (oral or parenteral) administration of a compound is not the same as topical administration. It is further well known in the art that various medicaments containing the same active ingredient can have vastly different indications in the treatment of various disease states. Applicants have previously provided (in the response file February 4, 2004) definitions of these terms from the Medline Plus, Merriam Webster medical dictionary as evidence that these two routes of drug administration are not similar or equivalent. Thus, as noted by the Patent Office, Bankneider does not teach, suggest or make obvious all of the claim limitations of amended independent claims 1, 13, 36, and 41.

The Patent Office further cites York et al. which teaches methods of promoting healing of ocular wounds comprising the topical application of an aldose reductase inhibitor to the eye (abstract). York et al. teaches that the route of administration is topically to the eye (column 2, lines 10-11). As noted by the Patent Office in the Action mail November 2, 2007 and again in the Advisory Action mailed March 19, 2008 "York teaches in the background of the invention 'these aldose reductase inhibitors can be applied **topically to the eye** or systemically to the diabetic to promote wound healing when indicated (col. I lines 35-40) [emphasis added].'"

Thus, as admitted by the Patent Office, York does not teach topical administration to the dermis/epidermis because as discussed above, it is well know that the eye does not contain dermal and epidermal cells.

The Patent Office goes on to assert that York teaches "aldose reductase inhibitors are also suitable and effective in treatment through carrier systems appropriate for topical **and** ocular administration." This assertion appears to suggest that York distinguishes **between** topical and ocular administration. The Patent Office directs the Applicant to column 2, lines 1-67 as evidence for this assertion. Applicants previously and now currently note that nowhere in this cited section does York teach aldose reductase inhibitors for topical **and** ocular administration. York merely teaches administration "**topically to the eye**" (line 11); "delivery of the involved aldose reductase inhibitors for corneal wound healing" (lines 27-28); "**ocular administration**" (line 31); "**topical, ocular formulations**" (line 45); and "ophthalmic indications" (line 67). Applicants pointed this out to the Patent Office in the response file February 4, 2208 and the Patent Office has provided no clarification on this matter in the Advisory Action mailed March 19, 2008. Thus, Applicants reiterate that York only teaches administration topically to the eye and not topically to the dermis or epidermis as recited in the instantly pending claims.

Finally, the Patent Office asserts that "the York reference teaches the equivalence of topical and systemic delivery;" however, the Patent Office still has provided no specific citation in York for this assertion. Furthermore, given that York only teaches systemic and ophthalmic administration, York cannot be asserted to teach the equivalence of systemic and topical skin administration. In fact, as noted in the DiPiro reference cited by the Patent Office, "the eye, with its unique structure and function, is an extremely sensitive organ" (page 43, last paragraph) while "the skin provides an effective barrier to the usage of substances into as well as out of the body" (page 41, 2nd paragraph). Thus, is it clear from the Patent Office's reference, that based upon the significant differences which exist between the eye and the skin, topical ophthalmic and topical skin administration are **not** equivalent and neither is equivalent to systemic administration. Given that York only teaches systemic or ocular administration and the eye does not contain dermis and epidermis, York et al. does not teach, suggest or make obvious "producing **a wound in the dermis or epidermis** of a diabetic animal; exposing the wound to an aldose reductase inhibitor compound by topical application of the compound to the wound, **wherein the topical application is to dermis or epidermis**" as recited in

independent claims 1, 13 ,36, and 41. Thus, York et al does not cure the deficiency of Bankneider.

The Patent Office further cites DiPiro et al. which is asserted to "show that it is well within the purview of one of ordinary skill in the art to prepare a topical or ophthalmic formulation, once in possession of the active ingredient." The Patent Office further asserts that "converting a[n] ophthalmic to a topical composition is a matter of optimizing the carrier system." Applicants have previously noted that, in fact, DiPiro teaches that topical compositions for use on the skin and ocular compositions for use on the eye are not equivalents and, as discussed above, notes the unusual and specific nature of both ocular preparations and skin preparations. DiPiro states that "the eye, with its unique structure and function, is an extremely sensitive organ" (page 43, last paragraph) while "the skin provides an effective barrier to the usage of substances into as well as out of the body" (page 41, 2nd paragraph). Thus, even the art cited by the Patent Office (DiPiro et al.) teaches that topical and ophthalmic preparations are not equivalents. Furthermore, the ability to prepare a topical or ophthalmic composition once in possession of the active ingredient does not provide any information or assurance as to the efficacy of the preparations. It is well know to those of ordinary skill in the art that just because an active ingredient is effective when administered opthalmically, does not necessary mean that the same active ingredient is effective when administered topically to the skin (Sodi et al.,2003, J. Dermatol. 30(9):697-700). For example, Applicants have previously provided an article which demonstrates that brimonidine tartate is an effective active ingredient for the treatment of glaucoma and ocular hypertension when administered opthalimically, but is ineffective when administered systemically and results in dermatologic irritation when administered to the skin.

Applicants respectfully point out that Bankneider only teaches the efficacy of systemic administration of aldose reductase inhibitors and York only teaches the efficacy of ophthalmic administration of aldose reductase inhibitors. Neither of these references teach, suggest, or make obvious the efficacy of topical dermal and epidermal administration of aldose reductase inhibitors. The Patent Office is relying on impermissible hindsight, based upon the teachings of the instant application to assert obviousness that topical administration, to the skin, of aldose reductase inhibitor can be effective in wound healing of the dermis and

epidermis. DiPiro does not provide any specific teachings as to the efficacy of topical dermal and epidermal administration of aldose reductase inhibitors in wound healing and thus does not cure the deficiency of Bankneider and York. In fact, DiPiro teaches away from the idea that systemic, topical skin and topical ophthalmic compositions are equivalent and are similarly effective.

The Patent Office has provided no response to these arguments and evidence, nor has the Patent Office provided any contradictory evidence. In fact, the Patent Office has provided no response whatsoever and has merely repeated the same sentences from the Action mailed November 2, 2007 in the Advisory Action mailed March 19, 2008. Applicants respectfully request that the Patent Office respond to the specific arguments made by the Applicants in the instant response and the response filed February 4, 2008.

It is further noteworthy that the Patent Office has provided, in the previous Action or the Advisory Action, no reason why the skilled artisan would combine the teachings of the cited references, nor that such a combination would yield an invention having the claim limitations recited in independent claims 1, 13, 36, and 41.

Thus, none of the references cited by the Patent Office alone or in combination teach, suggest or make obvious **all the limitations** of independent claims 1, 13, 36, and 41. Thus, the Patent Office has not established a *prima facie* case of obviousness of claims 1, 13, 36, and 41 based on the cited references. Rejected claims 2-4, 6-7, 14-16, 18-19, 25-26, 28-31, 33-35, 37-39, and 42-46 are dependent on the independent claims and share the above noted limitations and thus the references cited by the examiner also do not render these claims obvious. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

B. Claims 1-4, 6-7, 13-16, 18-19, 25-26, 28-31, 33-35 and 36-46 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over York in view of FDA Guideline No. 38, Chen and DiPiro et al. The Applicants respectfully traverse the rejection. According to M.P.E.P. 706.02 (j)

> *To establish a prima facie case of obviousness,* ***three basic criteria must be met****. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to*

> *one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.* ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations****. The teaching or suggestion to make the claimed combination and* ***the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure****. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).* [emphasis added]

Instantly pending independent claims 1, 13, 36, and 41 all recite the following claim limitations:

a) *producing* ***a wound in the dermis or epidermis*** *of a diabetic animal;*

b) *exposing the wound to an aldose reductase inhibitor compound by topical application of the compound to the wound****, wherein the topical application is to dermis or epidermis****;…* [emphasis added]

None of the references cited by the Patent Office teach suggest or make obvious the noted claim limitations of independent claims 1, 13, 36, and 41. In fact, the Patent Office has provided no direction, argument, or suggestion that the cited references teach at least these claim limitations of independent claims 1, 13, 36, and 41.

The Patent Office cites York et al. which teaches methods of promoting healing of ocular wounds comprising the topical application of an aldose reductase inhibitor (abstract). York et al teaches that the route of administration is **topically to the eye** (column 2, lines 10-11). As noted by the Patent Office in the previous Action and the instant Advisory Action, "York teaches…these aldose reductase inhibitors can be applied **topically to the eye or systemically**.'" Thus, as admitted by the Patent Office, York does not teach topical administration to the dermis/epidermis as recited in the claims, because as discussed above, it is well know that the eye does not contain dermal tissue. The Patent Office further notes that "York fails to compare the efficacy of his compositions against other potentially useful agents." Thus, York fails to teach a number of the claim limitations of the independent claims, <u>including</u> the specific limitation of "producing a wound in the dermis or epidermis… exposing the

wound to an aldose reductase inhibitor compound by topical application of the compound to the wound, **wherein the topical application is to dermis or epidermis**" as noted above and the claim limitation noted by the Patent Office in this part of the rejection.

The Patent Office further cites Guideline No. 38, which is asserted to "to show the standard for assessing topical efficacy of candidate drugs." Guideline No. 38 is not asserted to teach "producing **a wound in the dermis or epidermis** of a diabetic animal; exposing the wound to an aldose reductase inhibitor compound by topical application of the compound to the wound, **wherein the topical application is to dermis or epidermis**" as recited in the independent claims 1, 13, 36, and 41. Thus, Guideline No. 38 does not cure the deficiency of York, Bankneider, and DiPiro as addressed in section A above and, as stated in the MPEP, "*the prior art reference (or references when combined) must teach or suggest **all the claim limitations**.*"

The Patent Office cites Chen as an example of Guideline No. 38. Chen is not asserted to teach "producing **a wound in the dermis or epidermis** of a diabetic animal; exposing the wound to an aldose reductase inhibitor compound by topical application of the compound to the wound, **wherein the topical application is to dermis or epidermis**" as recited in the independent claims 1, 13, 36, and 41. Thus, Chen does not cure the deficiency of York, Bankneider, DiPiro, and Guideline No. 38 as addressed in section A above and, as stated in the MPEP, "*the prior art reference (or references when combined) must teach or suggest **all the claim limitations**.*"

Finally, the Patent Office again cites DiPiro as showing "that it is well within the purview of one or ordinary skill in the art to prepare a topical or opthalmic formulation, once in possession of the active ingredient." The reference has been addressed in detail in section A above. As previously noted, DiPiro, teaches that topical compositions for use on the skin and ocular compositions for use on the eye are not equivalents and, notes the unusual and specific nature of both ocular preparations (page 43, last paragraph) and skin preparations (page 41 second paragraph). DiPiro does not provide any specific teachings as to the efficacy of topical dermal and epidermal administration of aldose reductase inhibitors in wound healing and thus does not cure the

deficiency of Bankneider, York, Guideline No. 38 and Chen. In fact, as previously noted, DiPiro teaches away from the idea that systemic, topical skin and topical ophthalmic compositions are equivalents. Furthermore, the Patent Office has provided no response in the Advisory Action mailed March 19, 2008 to the fact that DiPiro teaches away from the instant claims and has merely repeated the same sentences from the Action mailed November 2, 2007.

Thus, none of the references cited by the Patent Office alone or in combination teach, suggest or make obvious **ALL the limitations** of independent claims 1, 13, 36, and 41 as required by the MPEP. Thus, the Patent Office has not established a *prima facie* case of obviousness of claims 1, 13, 36, and 41 based on the cited references. Rejected claims 2-4, 6-7, 14-16, 18-19, 25-26, 28-31, 33-35, 37-39, and 42-46 are dependent on the independent claims and share the above noted limitations and thus the references cited by the examiner also do not render these claims obvious. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

3. CONCLUSION

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner Soroush believes it to be helpful, he is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
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